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Short Stature in a Mother and Daughter With Terminal Deletion of Xp22.3

Eberhard Schwinger, Martin Kirschstein, Monika Greiwe, Thora Konermann, Ulrike Orth, and Andreas Gal

Institut für Humangenetik (E.S., M.G., T.K.) and Klinik für Pädiatrie (M.K.), Medizinische Universität zu Lübeck, and Institut für Humangenetik, Universitäts-Krankenhaus Eppendorf, Hamburg (U.O., A.G.), Germany

Short stature in females is often caused by hemizygosity for the terminal portion of Xp due to monosomy X or a deletion. We report on a mother and daughter with short stature as sole phenotypic abnormality and deletion of bands Xp22.32-p22.33 demonstrated by classic and molecular cytogenetic analysis. In both individuals, the deleted X chromosome was late replicating. Molecular analysis suggested that the deletion is terminal and the breakpoint was localized between the STS and DXS7470 loci in Xp22.32. Chromosome analysis is often done on females with short stature to exclude Ullrich-Turner syndrome. Small deletions, terminal or interstitial, are easily missed by conventional cytogenetic investigation; thus molecular analyses are useful to detect those cases.

KEY WORDS: deletion, Xp, short stature, X-inactivation pattern

INTRODUCTION

Normal female sexual differentiation and ovarian function depend on the presence of two normal X chromosomes. Females with only one X chromosome (45,X) show the clinical picture of the Ullrich-Turner syndrome (UTS) characterized by hypoplasia of external and internal genitalia, gonadal streaks, and short stature as one of the most prominent somatic symptoms. In females with a normal and a rearranged X chromosome, clinical findings vary according to the involvement of the short or long arm. Based on the analysis of cases with isochromosomes for Xp or Xq it has been suggested that UTS is due to the absence of Xp, whereas somatic symptoms are less pronounced if the long arm of the X chromosome is absent; in such cases functional deficiencies such as early menopause are more common.

Heterozygous terminal deletions of the distal short arm of the X chromosome have usually limited phenotypic manifestations in females and can therefore be underdiagnosed. Here we report cytogenetic and molecular findings in a mother and daughter with 46,X,del(X)(p22.32) and short stature.

CLINICAL REPORT

The proposita, now 10 years old, was born to a 19-year-old mother and a 20-year-old father (Fig. 1). She presented for evaluation of short stature (127.5 cm [3rd centile, NCHS Growth Charts]; her weight was 36.5 kg [75th centile]). According to outside medical records, her growth had been on the 3rd centile throughout her life. Assuming a similar course of growth, the expected adult final height of the girl is about 156 cm. Her medical history was otherwise unremarkable.

On physical examination, all findings were normal. No signs of onset of puberty (Tanner stage 1) were found. All routine laboratory measurements gave values within the normal range including insulin-like growth factor (IGF) and insulin-like growth factor binding protein 3 (IGF-BP3). Bone age corresponded to chronological age. Roentgenograms of hands showed no pathologic changes.

Aside from her short stature, the mother's development was normal. Menarche occurred at the age of 13 years and menstrual cycles were regular. After the birth of her daughter, she developed obesity (100 kg). Two years after the birth of her first child she had a missed abortion. The mother is 150 cm and her sister is 168 cm tall. Their mother, i.e., the grandmother of the proposita, is 170 cm tall, while the father's height is 180 cm (Fig. 1). Target height (TH) gives a person's expected final height calculated from the corresponding values of the parents [for further details, see Ogata et al., 1992a,b]. TH of the mother (and her sister) is 170.5 cm with a 95% confidence interval (TR, target range) of 162.2–178.5 cm. This means that while the height of the mother's sister is quite close to the expected value, there is a deficit of 20.5 cm between TH and actual height of the mother, which is even below her TR.

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Address reprint requests to Prof. Dr. med. Eberhard Schwinger, Institut für Humangenetik, Medizinische Universität zu Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany.

Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

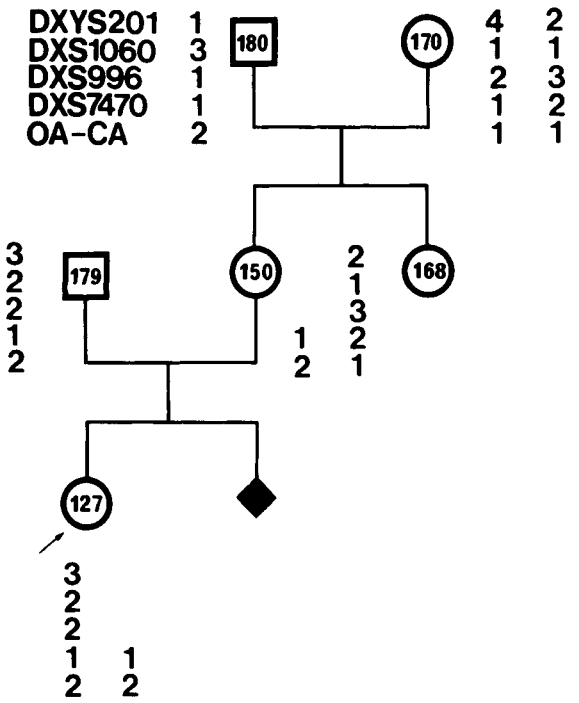

Fig. 1. Pedigree of the family. Numbers within the symbols give the height of family members in cm. Numbers on the left or right sites of each pedigree symbol denote the different alleles detected at the various loci and are arranged according to the most likely haplotypes.

CYTOGENETIC STUDIES

Cytogenetic analysis was done on the proposita and her parents. All analyses were performed on PHA-stimulated synchronized blood cultures according to Yunis [1976] and using amethopterin as synchronising agent. After GTG-banding (Fig.2b), the patient showed the karyotype 46,X,del(X)(p22.3). The mother was found to carry the same deletion (Fig.2a). The father's karyotype was normal (not shown). The replication pattern of the X chromosomes using reverse banding with BrdU and acridine orange (RBA-banding) showed the deleted X chromosome being consistently late replicating both in the index case and her mother (Fig. 2a,b). Fluorescence in situ hybridization (FISH) using a cosmid probe (Oncor-Amersham) hybridizing to the STS gene on Xp22.3 revealed no signal on the deleted X chromosome (Fig.3).

MOLECULAR STUDIES

We have genotyped the index case, her parents, and maternal grandparents for several PCRable dinucleotide-repeat type polymorphisms with loci in Xp22.3. The data, summarized in Figure 1, show Mendelian inheritance of the polymorphic alleles at the DXS7470 (mapped close to KAL) and OA loci. However, an apparent incompatibility exists for the index case in that she carries only paternal alleles for the X-specific loci DXS996 and DXS1060 and the pseudoautosomal locus DXYS201. In contrast, the mother carries only maternal alleles at these latter three loci. All these inconsistencies can be explained by assuming that both the index case and her mother carry a heterozygous terminal deletion of Xp22.3 with a breakpoint between DXS7470 and DXS996. Since a heterozygous deletion of the STS gene was suggested by FISH analysis, the breakpoint may be proximal to/within the STS locus in Xp22.32. As the maternal grandmother shows a heterozygous pattern for the polymorphisms at DXYS201 and DXS996, she can not carry the same deletion. Segregation data suggests that the deletion occurred de novo during spermatogenesis in the maternal grandfather of the index case (Fig.1).

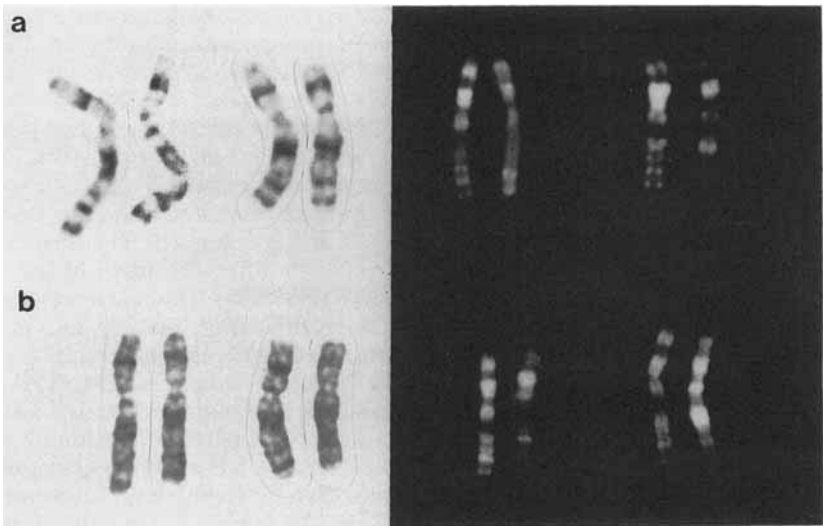

Fig. 2. GTG- (left) and RBA-banding (right) of the normal (left) and rearranged (right) X chromosomes of the index case (**b**) and her mother (**a**). The X chromosome with the deletion is late replicating (RBA banding).

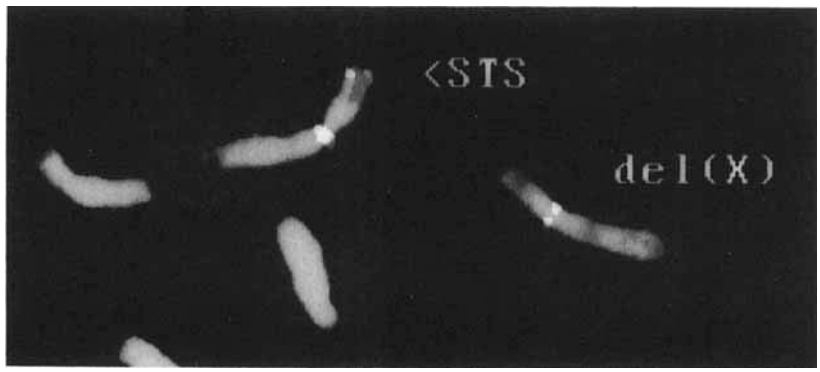

Fig. 3. Fluorescence in situ hybridization using an X-specific centromere probe and a cosmid containing (part of) the human gene for steroid sulfatase (STS) after propidium iodide staining.

DISCUSSION

Here we describe a de novo terminal deletion with breakpoint in Xp22.32 associated with short stature as the sole recognizable phenotype in a mother and daughter. Genotype-phenotype analysis of patients with X chromosome rearrangements suggests the presence of a "growth gene" in the pseudoautosomal region [Henke et al., 1991; Ogata et al., 1992a,b]. This putative growth gene was localized between DXYS15 and DXYS20 by deletion mapping [Ogata et al., 1995]. DXYS20 is very close to the telomere while DXYS15 maps about 800 kb proximal to it, defining the maximal size of the region harbouring the growth gene. Our molecular data suggest, but do not confirm, that the deletion is terminal in our two cases, i.e., that they are hemizygous for the growth gene. The most distal locus studied by us and shown to be deleted is DXYS201 which maps in the distal part of the pseudoautosomal region about 400 kb proximal to the telomere [Rappold et al., 1994].

Recently, Schaefer et al. [1993] constructed a high-resolution physical map based on the analysis of 50 patients with various rearrangements involving Xp22. One may speculate that the deletion described by us is the consequence of a non-homologous recombination that occurred in male meiosis between the X chromosome and another chromosome, the Y chromosome, or an autosome. Indeed, there is a cluster of Xp/Yq translocations in the panel of Schaefer et al. [1993] with breakpoints distal to KAL/DXS7470, i.e., in the same region as in our case. Extensive sequence homology exists between Xp22.3 and Yq11 due to the presence of Y-chromosomal pseudogenes of several functional genes mapped on Xp22.3. Similarly, highly homologous low-copy repetitive elements ("S232-like" sequences) have been identified and mapped to two distinct regions, approximately 2.0 Mb apart, on the X chromosome in p22.3 and, in addition, to Yq [Yen et al., 1990]. It has been suggested that non-homologous recombinations between these S232-like sequences is a frequent cause of (larger) interstitial deletions found in about 80% of patients with X-linked ichthyosis (STS deficiency). Therefore one may speculate that non-homologous recombinations between S232-like elements may also be causative both for interstitial and terminal deletions and/or Xp/Yq translocations.

Several genes implicated in different X-chromosomal diseases have been mapped in the region Xp22.32-pter, e.g., that for Kallmann syndrome, X-chromosomal ichthyosis (STS deficiency), ocular albinism, or chondrodysplasia punctata. In some of these traits, carriers may also present with mild manifestations due to random X-inactivation. However, the mother and daughter described here do not show any signs of a carrier manifestation for the disorders mentioned above, most likely due to the non-random inactivation of the rearranged X chromosome. The short stature represents a dosage effect, i.e., the absence of one copy of the putative growth gene assigned to the pseudoautosomal region which escapes X-inactivation.

Small deletions, terminal or interstitial, can easily be missed by conventional cytogenetic investigation; thus, molecular analyses are useful to detect those cases.

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